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Review

The potential significance of elevated vitreous sodium levels at autopsy

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ABSTRACT

Elevated levels of sodium that may be detected in the analysis of post-mortem fluid samples may arise from a wide variety of organic illnesses and environmental factors that have caused either water depletion or solute gain. When hypernatraemia is suspected at autopsy a careful history is required with particular emphasis on pre-existing medical conditions such as renal or gastrointestinal disease. In addition, detailed information is required on the circumstances of death, including any clinical symptoms and signs that the deceased may have manifested, or medical procedures such as dialysis, colonoscopy or intravenous fluid replacement. Reduced intake of fluid may be associated with cognitive or physical impairment or may result from environmental depletion (the latter may be a manifestation of inflicted injury). Both central and nephrogenic diabetes insipidus may result in the loss of excessive amounts of hypotonic fluid. This may also occur following diuretic use, or be due to gastroenteritis or burns. Hypernatraemia may be a marker of excessive salt/saline ingestion and/or administration and may occur accidentally or as a manifestation of child abuse. Given the range of possible etiologies, hypernatraemia may be a significant autopsy finding that requires explanation.

1. Introduction

The normal serum sodium is generally maintained at concentrations between 135 and 145 mmol/L despite considerable variations in water and salt intake, with elevation in serum sodium, hypernatraemia, referring to concentrations exceeding 145 mmol/L.[1,2] The serum concentration reflects the total body exchangeable sodium relative to water content.[3] Although there is considerable literature on hypernatraemia in clinical settings, less has been written on the potential significance of this finding after death. The following paper provides an overview of normal sodium metabolism with an analysis of possible causes of hypernatraemia that may be encountered at autopsy.

2. Normal water and sodium balance

Water metabolism is predominately regulated through the arginine vasopressin (AVP) system in response to changes in plasma osmolarity. AVP secretion from the posterior pituitary gland is stimulated by osmoreceptors located in the anterior hypothalamus and also by baroreceptors located in the carotid arteries and the aortic arch, in response to decreases in mean arterial pressure or blood volume. Circulating AVP binds to AVP V_2 receptors in the nephrons of the kidney leading to aquaporin-2 water channel insertion into collecting duct cell membranes. This allows free water reabsorption and antidiuresis.[4] An intact hypothalamopituitary axis is, therefore, necessary to prevent hypernatraemia.

In addition to causing water retention by increasing the concentration of urine, hypothalamic osmoreceptors stimulate the sensation of thirst in response to quite small increases (1–2%) in plasma osmotic pressure.[5] Renin, and its effector peptide, angiotensin II, which is released in response to decreased renal perfusion pressure and increased sodium delivery of filtered sodium to the macula densa cells also stimulate thirst and increases water intake.[6]

The control of sodium homeostasis is closely linked to water balance, and as well as stimulating thirst, angiotensin II also stimulates the release of aldosterone from the adrenal cortex. This binds to mineralocorticoid receptors on the principal cells of the renal cortical collecting ducts increasing the number and activity of sodium channels/pumps, and thereby increasing sodium reuptake.[6]

3. Clinical manifestations of hypernatraemia

Although hypernatraemia has been documented in only 1% of hospitalised patients, the mortality rate is high, ranging from 42% to 60%.[7] The primary clinical manifestations are caused by cerebral dehydration with resulting central nervous system depression. Patients with hypernatraemia demonstrate non-specific findings such as impaired mental function, confusion, abnormal speech

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and obtundation, with stupor or coma in severe cases.[3] Due to the non-specific nature of the clinical manifestations the symptoms and signs cannot be reliably used to identify hypernatraemia nor to estimate the severity of the sodium imbalance. Cases occur when the thirst mechanism is abnormal or access to water is limited, the latter occurring in infants, patients with mental or physical handicaps, following surgery or with intubation.[8]

4. Post-mortem changes

Electrolyte levels alter in the post-mortem period, the degree of change depending on the conditions of storage of the body, the post-mortem interval, the body fluid being sampled and the particular analyte being evaluated. Changes depend on the effects of cellular hypoxia that lead to increased cell membrane and blood vessel wall permeability, and reduction in ATP stores that prevents electrolyte pumps maintaining physiological cell membrane electrical gradients. These factors result in merging of intra- and extracellular fluid and their respective electrolytes that, coupled with autolysis and cell disintegration, lead to important and unpredictable changes in electrolyte contents in post-mortem samples.[9]

The vitreous humor (VH) of the eye represents an isolated fluid that is less vulnerable to rapid chemical changes or contamination than the blood.[10] It is also superior to other body fluids, such as cerebrospinal, pericardial and joint fluid, as it undergoes post-mortem changes more slowly and is technically easier to obtain.[11] Analysis of vitreous humor electrolytes, urea nitrogen and glucose has provided significant information on both the cause and time of death in 5% or more of cases.[11] Although not usually presenting difficulties with processing, on occasion vitreous may be viscous or contaminated with retina. Under these circumstances one of our laboratories has found that dilution with sterile water and use of flame photometry rather than an ion specific electrode may be an effective alternative method.

While potassium increases in the post-mortem period, particularly in blood if there is hemolysis, sodium levels in the vitreous humor have been found to be relatively stable, although serum sodium has been shown to decrease after death at an average rate of 0.9 meq/L.[10,11] However, it is still not completely clear how well post-mortem vitreous humor sodium levels match antemortem serum measurements, and post-mortem reference ranges need to take into account the age, sex and medication use of the deceased.[12] It is also unclear how long it takes for depressed or elevated serum levels to equilibrate with the vitreous. In addition, levels may vary according to the different analytical procedures and instruments used.[13] For this reason it has been suggested that each laboratory should develop its own set of reference intervals depending on these factors until a uniform analytical method is decided upon. However, the decrease in sodium levels after death means that an elevated level is more likely to be of significance.

5. Hypernatraemia at autopsy

Elevation of serum sodium levels may result from either water depletion or solute gain[14] the causes of which may be due to either environmental or endogenous factors. When hypernatraemia is suspected at autopsy a careful history is required with particular emphasis on pre-existing medical conditions such as renal or gastrointestinal disease. In addition detailed information is required on the circumstances of death, including any clinical symptoms and signs that the deceased may have manifested and the environmental temperature.

The simplest cause of hypernatraemia is water depletion due to an inadequate intake. This may result from a variety of circumstances including a lack of environmental water. This occurs accidentally in individuals who die of 'exposure' in desert country, contributed to by excessive sweating if the ambient temperatures are elevated. At autopsy such individuals are often markedly putrefied due to hot weather and a failure to discover the body in a timely manner, thus precluding meaningful electrolyte analysis. If the body is found soon after death there will be evidence of dehydration with sunken eyeballs, turgid skin and subcutaneous tissues and dry serosal surfaces.[15,16] Vitreous humor sodium levels of greater than 155 meq/L have been cited as evidence of dehydration.[17]

Children and infants who are in a dependent situation are also at risk of death from reduced water intake if the adult who is looking after them is socially isolated and becomes incapacitated. Such was the case of a three-year-old boy whose grandfather died of ischaemic heart disease. He survived for some time after his grandfather but eventually succumbed to dehydration. At autopsy his vitreous humor sodium was 181 mmol/L.[18] Deliberate deprivation of water may occur in captive situations and may occur in cases of extreme child abuse. The autopsy assessment of dehydration is sometimes difficult in children who have been starved to death as marasmic skin has a doughy feel similar to that in dehydration. In these instances vitreous sodium levels can be helpful in determining whether fluid deprivation played a role in the terminal episode.

Although water may be readily available, intake may be significantly reduced in those with reduced thirst due to blunting of the thirst response with age due to osmoreceptor dysfunction, or to significant illness.[19,20] The elderly may be particularly at risk in hospitals due to long fasts required for certain investigations, an inability to pour their own water from bedside jugs, and increased likelihood of conditions such as diabetes or hypercalcaemia that result in increased urination and reduced efficacy of the kidneys to concentrate urine. A reduction in water intake may also accompany cognitive dysfunction in dementia; fluid/electrolyte imbalance has been found to be three times more common amongst patients with dementia compared to those without.[21] In individuals with significant disease who require a high level of nursing support, questions may be asked as to the adequacy of care. Unfortunately this may be an issue that is not contributed to by post-mortem sodium levels as agonal dehydration may be a normal component of a number of terminal diseases. It may also occur if nasogastric feeding is terminated in individuals in vegetative states who are unable to fed themselves.[22,23]

Other barriers to adequate water intake include both physical abnormalities and neurological disorders such as severe motor impairment from cerebral palsy or high spinal cord trauma. Babies with a cleft palate often have difficulties with suckling that may lead to neonatal hypernatremic dehydration.[24]

A variety of medical conditions may result in elevated serum sodium due to excessive fluid loss, most of which are associated with a concomitant reduction in oral intake. Both central and nephrogenic diabetes insipidus may lead to concentrated serum electrolytes, as may diuretic states induced by drugs, or renal disorders such as acute tubular necrosis. Central diabetes insipidus is due to a deficiency of AVP secretion from the posterior pituitary.[4] If this is suspected at autopsy careful examination of the brain and spinal cord should be undertaken for evidence of predisposing lesions such as cerebrovascular accident, tumor, sarcoidosis or, or spinal cord injury.[25] This condition is fairly rare, occurring in only 1 in 25,000 individuals as 85% of the AVP-secreting magnocellular neurons must be damaged before the condition can manifest.[4]

Nephrogenic diabetes insipidus is caused by end-organ resistance to the antidiuretic effect of AVP[4] that may be due to an hereditary mutation in the gene that codes for aquaporin V2.[26] Alternatively it may be acquired due to conditions such as hypokalaemia, hypercalcaemia or medication use (e.g. lithium and deme-

clocycline). Serum AVP measurements are useful clinically in distinguishing central and nephrogenic diabetes insipidus.[4]

Water may also be lost due to osmotic diuresis, the most common cause of which is hyperglycaemia due to poorly controlled diabetes mellitus.[8] Diuretics may also predispose an individual to hypernatraemia due to hypotonic fluid loss; although diuretics are associated with both renal sodium and water loss, free water is lost to a greater extent.[27]

Non-renal fluid losses from gastrointestinal causes such as vomiting or diarrhoea may also cause hypernatraemia[28], as may fluid loss from hyperventilation. Hypernatraemia in infants is commonly caused by diarrhoea.[1]

Iatrogenic causes of elevated serum sodium include excessive nasogastric suction[1] and renal dialysis. Fatal hypernatraemia has also been reported following elective colonoscopy when the preparation solution has precipitated massive diarrhoea and emesis, followed by metabolic alkalosis, shock and respiratory arrest.[29] Oncology patients may be susceptible to hypotonic fluid loss as a result of frequent diarrhoea and emesis.[30]

Individuals doing heavy manual labour in hot conditions may also lose excessive amounts of fluid through sweat, hence the need for adequate electrolyte replacement, however hypernatraemia may occur if there is overly rapid administration of sodium salts (aimed at combating hyponatraemia).[31] This also applies to members of disaster victim identification teams who may have to travel at short notice to tropical environments. Individuals with significant burns at all ages may also lose excessive amounts of fluid and die.[32]

An alternative mechanism for hypernatraemia is increase in solute load, most often derived from an increased intake of sodium. This may occur in infants and the very young for a variety of reasons including the inadvertent administration of concentrated infant formula that has not been adequately diluted.[33] The deliberate administration of salt or concentrated food may also occur in cases of child abuse that have been associated with factitious illness by proxy, or so-called Munchausen syndrome by proxy.[34–36] Neonatal hypernatremic dehydration has been attributed to the consumption of breast milk that is high in sodium.[37,38]

Hypernatraemia may occur following the ingestion of other substances including sodium hypochlorite.[39] On occasion, ingestion of excessive quantities of salt water may occur as part of obscure rituals, such as the case of a woman suffering from severe postpartum depression who took part in an 'exorcism' that involved drinking large quantities of salt water. On admission to hospital her serum sodium concentration was 255 mmol/L; death followed shortly afterwards due to severe hypernatraemia.[40] Fatal hypernatraemia may follow the consumption of salt solutions to induce emesis.[41]

Fatal hypernatraemia also occurs in salt-water drownings[42] and at autopsy elevation in left ventricular and vitreous sodium levels may be found. This has been attributed to redistribution of inhaled saltwater from the alveoli into the circulation with resultant hemoconcentration.[43] It is also possible that elevated vitreous sodium levels may occur in bodies that have been immersed in saltwater for some time due to passive diffusion.

Ingestion is not the only means of sodium entering the body. For example a young diabetic boy developed hypernatremic hemorrhagic encephalopathy after mistakenly being infused with hypertonic solution instead of insulin[44] and an infant has been reported who died from hypernatraemia after having an over-the-counter enema.[45] An unusual case of fatal hypernatraemia was caused by an amniotic fluid embolism resulting from a saline-induced abortion.[46]

Table 1
Possible conditions and predisposing factors that may be associated with hypernatraemia at autopsy.

1. Water depletion (decreases in total body water in excess of body solute)
(1) *Insufficient water intake*
i. Lack of availability of water
a. Environmental
b. Age-related
c. Inflicted
ii. Reduced thirst (hypodipsia)
a. Osmoreceptor dysfunction
b. Age
c. Illness
iii. Reduced water intake
a. Cognitive dysfunction
b. Motor impairment
(2) *Hypotonic fluid loss*
i. Renal: diabetes insipidus
a. Reduced AVP secretion (central diabetes insipidus, osmoreceptor dysfunction)
b. Reduced AVP effect (nephrogenic diabetes insipidus)
ii. Renal: other fluid losses
a. Osmotic diuresis (hyperglycaemia, mannitol)
b. Diuretic drugs (furosemide, ethacrynic acid, thiazides)
c. Postobstructive diuresis
d. Diuretic phase of acute tubular necrosis
iii. Non-renal fluid loss
a. Gastrointestinal (vomiting, diarrhoea, nasogastric suction)
b. Cutaneous (sweating, burns)
c. Pulmonary (hyperventilation)
d. Peritoneal dialysis
* Most hypotonic fluid losses will not produce hyperosmolality unless insufficient free water is ingested or infused to replace the ongoing losses; therefore these disorders also involve a component of insufficient water intake
(3) *Miscellaneous*
2. Solute excess (increases in total body solute in excess of body water)
(1) *Sodium*
i. Sodium administration (NaCl, $NaHCO_3$)
a. Iatrogenic
b. Accidental
c. Inflicted
ii. Saltwater drowning
(2) *Other*
i. Hyperalimentation (intravenous/parenteral)
(3) *Miscellaneous*

6. Conclusions

Hypernatraemia may be found at autopsy in wide range of a medical conditions and also following misadventure (Table 1). Elevated sodium levels should therefore be suspected in cases where there is evidence of reduced fluid intake, and post-mortem levels should be measured. Although changes occur in post-mortem sodium levels these often remain stable for sufficient time to provide information that may be useful in determining the mechanism of death. In addition to reduced intake of fluid, hypernatraemia may be a marker of excessive fluid loss and also of increased sodium consumption. Individuals at the extremes of life may be at particular risk, and also those who have undergone certain medical procedures such as dialysis, and colonoscopy, or who have had intravenous fluid replacement or hyperalimentation. The possibility of inflicted injury or feeding error should be suspected in infants who present with markedly elevated levels of sodium.

Conflict of Interest

None declared.

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